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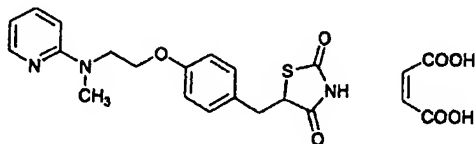
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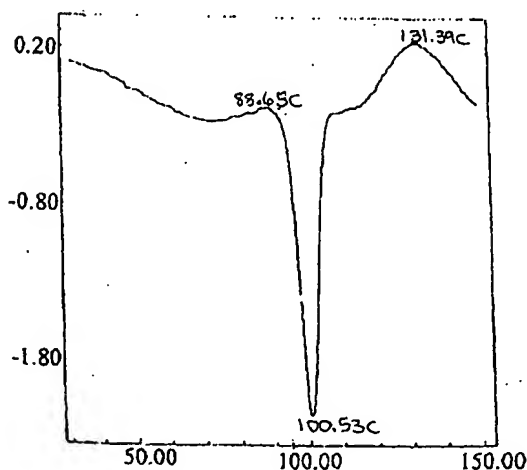
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(54) Title: NOVEL POLYMORPHIC FORMS OF 5-[4-[2-[N-METHYL-N-(2-PYRIDYL)AMINO]ETHOXY]BENZYL] THIAZOLIDINE-2,4-DIONE MALEATE AND PROCESS FOR THEIR PREPARATION



(I)



(57) Abstract: This invention relates to novel polymorphic/pseudopolymorphic forms of 5-[4-[2[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl] thiazolidine-2,4-dione maleate having formula (I). The invention also relates to a pharmaceutical composition comprising the novel polymorphic form or their mixture and a pharmaceutically acceptable carrier. The polymorphic forms of the present invention are more active, as antidiabetic agent, than the hitherto known 5-[4-[2-[N-(2-methyl-N-(2-pyridyl)amino]ethoxy]benzyl] thiazolidine-2,4-dione maleate.



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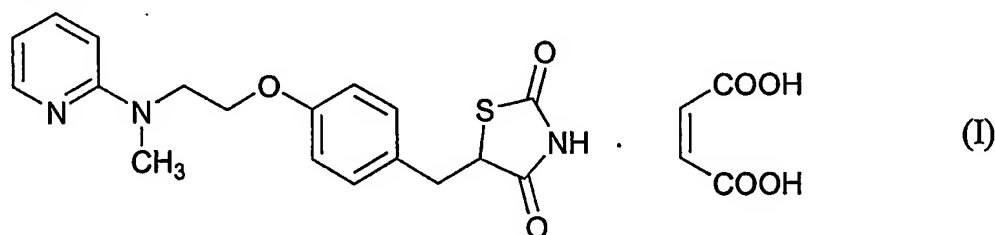
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NOVEL POLYMORPHIC FORMS OF 5-[4-[2-[N-METHYL-N-(2-PYRIDYL)AMINO]ETHOXY]BENZYL] THIAZOLIDINE-2,4-DIONE MALEATE
AND PROCESS FOR THEIR PREPARATION

Field of the Invention

5 This invention relates to novel polymorphic/pseudopolymorphic forms of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate and its stereo- isomers having formula (I). The invention also relates to a pharmaceutical composition comprising the novel polymorphic form or their mixture and a pharmaceutically acceptable carrier. The polymorphic forms of the present invention are
10 more active, as antidiabetic agent, than the hitherto known 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy] benzyl] thiazolidine-2,4-dione maleate.



The present invention also relates to a process for the preparation of various polymorphic/pseudopolymorphic 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy] benzyl]thiazolidine-2,4-dione maleate, having the formula (I) shown below. The
15 polymorphic forms prepared by the process of the present invention are more active, as an antidiabetic agent.

The polymorphic forms of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl] thiazolidine-2,4-dione maleate, of formula (I) defined above of the present invention
20 reduce blood glucose and has beneficial effect on coronary heart disease and atherosclerosis.

Out of the many drugs available for the treatment of diabetic ailments, the thiazolidine dione derivatives are very prominent and are considered as much superior effective constituents compared to the sulphonyl ureas. 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, one such thiazolidinedione
25 which exhibited euglycemic effect, was reported in the year 1988 by Beecham group England (EP 0306228A1) and created interest in the field, ever since.

The novel polymorphic forms of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy] benzyl]thiazolidine-2,4-dione maleate, of formula (I) defined above of the present

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invention are useful in reducing body weight and for the treatment and/or prophylaxis of diseases such as hypertension, coronary heart disease, atherosclerosis, stroke, peripheral vascular diseases and related disorders. The novel polymorphic forms of 5-[4-[2-[N-methyl-N-(2-pyridyl) amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, of formula (I) of the present invention can be used for the treatment of certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis and nephropathy. The novel polymorphic Forms of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl] thiazolidine-2,4-dione maleate, of formula (I) are also useful for the treatment and/or prophylaxis of insulin resistance (type II diabetes), leptin resistance, impaired glucose tolerance, dyslipidemia, disorders related to syndrome X such as hypertension, obesity, insulin resistance, coronary heart disease and other cardiovascular disorders. These novel polymorphic forms of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, of formula (I) may also be useful as aldose reductase inhibitors, for improving cognitive functions in dementia, treating diabetic complications, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), inflammatory bowel diseases, osteoporosis, myotonic dystrophy, pancreatitis, arteriosclerosis, retinopathy, xanthoma, inflammation and for the treatment of cancer. The novel polymorphic forms of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy] benzyl]thiazolidine-2,4-dione maleate, of formula (I) of the present invention are useful in the treatment and/or prophylaxis of the above said diseases in combination/con-comittant with one or more HMG CoA reductase inhibitors, hypolipidemic/hypolipoproteinemic agents such as fibric acid derivatives, nicotinic acid, cholestyramine, colestipol, probucol.

Background of the invention

The latest trend that has, of late, crept into the pharmaceutical industry is the studies on polymorphism in drugs and the difference in the activity of different polymorphic forms of a given drug. By the term polymorphism we mean to include different physical forms, crystal forms, crystalline / liquid crystalline / non-crystalline (amorphous) forms. This has especially become very interesting after observing that many antibiotics, antibacterials, tranquilizers etc., exhibit polymorphism and some/one of the polymorphic forms of a given drug exhibit superior bio-availability and consequently show much higher activity compared to other polymorphs. Sertraline, Frentizole, Ranitidine, Sulfathiazole, Indomethacine etc. are some of the important examples of

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pharmaceuticals which exhibit polymorphism. Polymorphism in drugs is a topic of current interest and is evident from the host of patents being granted. To cite a few, U.S. 5,700,820 discloses six polymorphic forms of Troglitazone, U.S. 5,248,699 discusses about five polymorphic forms of Sertraline hydrochloride while EP 014590 describes four polymorphic forms of Frentizole. EP 490648 and EP 022527 also deal with the subject of polymorphism in drugs.

European Patent No.0306338, International publication No. WO 94/25026 and U.S. Patent Application No. 5,646,169 describe that the relative configurations of the diastereomers have been determined by x-ray crystallographic analysis and that the crystal and molecular structure of the 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate is under preparation. The report does not touch upon the possibility/observation that 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]thoxy]enzyl]thiazolidine-2,4-dione maleate exists in different polymorphic forms. There is no published literature regarding such an observation till date. Polymorphism in drugs is a topic of current interest and is evident from the host of patents being granted to cite a few U.S. 5,248,699 discusses about five polymorphic forms of Sertraline hydrochloride while EP 014590, describes four polymorphic forms of Frentizole EP 490648 and EP 022527, six polymorphic forms of Troglitazone WO 97/27191 also deal with the subject of polymorphism in drugs. The fact that polymorphism in 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate has not been studied earlier coupled with the current interest in the field of polymorphism in drugs prompted us to take-up this investigation our observations and results from the subject matter of the present invention.

With a view to prevent/cure the chronic complications of diabetes, research is being conducted round the world in recent times. 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate is being considered today as one of the most effective anti-diabetic drugs which as a multi-purpose activity not only acting on diabetes itself but also on the reduction of the triglycerides and also on the accompanying complications mentioned above. Indeed the said 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate is emerging as the second drug candidate of euglycemic class of antidiabetic agents.

With an objective to develop novel polymorphic forms for lowering cholesterol and reducing body weight with beneficial effects in the treatment and/or prophylaxis of

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diseases related to increased levels of lipids, atherosclerosis, coronary artery diseases, Syndrome-X, impaired glucose tolerance, insulin resistance, insulin resistance leading to type 2 diabetes and diabetes complications thereof, for the treatment of diseases wherein insulin resistance is the pathophysiological mechanism and for the treatment of
5 hypertension, with better efficacy, potency and lower toxicity, we focused our research to develop new polymorphic forms effective in the treatment of the above mentioned diseases. Effort in this direction has led to polymorphic forms having the formula (I).

Another objective of the present invention is to provide polymorphic forms of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, their
10 stereoisomers, their pharmaceutically acceptable solvates and pharmaceutical compositions containing them or their mixtures which may have agonist activity against PPAR α and/or PPAR γ , and optionally inhibit HMG CoA reductase, in addition to having agonist activity against PPAR α and/or PPAR γ .

Another objective of the present invention is to provide novel polymorphic forms
15 of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, their stereoisomers, pharmaceutically acceptable solvates and pharmaceutical compositions containing them or their mixtures having enhanced activities, without toxic effect or with reduced toxic effect.

Yet another objective of the present invention to provide a process for the
20 preparation of novel polymorphic forms of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, their stereoisomers, pharmaceutically acceptable solvates.

Still another objective of the present invention is to provide pharmaceutical compositions containing novel polymorphic forms of 5-[4-[2-[N-methyl-N-(2-pyridyl)
25 amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, solvates or their mixtures in combination with suitable carriers, solvents, diluents and other media normally employed in preparing such compositions.

Summary of the Invention

The present invention relates to an observation that 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate exhibits polymorphism,
30 which has not been reported till date. The polymorphic Forms I, II, III and IV are obtained from different solvents like ethanol, acetone, methanol and 1,4-dioxane respectively.

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From powder X-ray diffraction studies Forms I, II, III and IV are found to be crystalline in nature.

DSC of the polymorphic Form I shows melting endotherm at 100.53°C. Form II displays endotherm at 127.67°C. Form III exhibits melting endotherm at 126.41°C and
5 Form IV exhibits endotherm at 125.39°C.

All these polymorphic forms were proved to be identical in solution as evident from Nuclear Magnetic Resonance (NMR), Ultra Violet (UV) & Mass spectral data. On the other hand, solid state techniques like Differential Scanning Calorimetry (DSC), Powder X-Ray Diffractometry (XRD) and Infra Red spectroscopy (IR) revealed the
10 difference among these forms.

Brief Description of the Figures

X-ray powder diffraction pattern has been obtained on a Rigaku D/Max 2200 model diffractometer equipped with horizontal goniometer in $\Theta/2\ \Theta$ geometry. The copper K α ($\lambda=1.5418\text{\AA}$) radiation was used and the sample was scanned between 3-45
15 degrees 2Θ .

Differential scanning calorimeter was performed on a Shimadzu DSC-50 equipped with a controller. The data was collected on to a Pentium PC using a Shimadzu TA-50 software. The samples weighed in aluminum cells were heated from room temperature to 220°C at a heating rate of 5°C /min. The empty aluminum cell was used
20 as a reference. Dry nitrogen gas was purged through DSC cell continuously throughout the analysis at a flow rate of 30 ml/min.

Fig 1 is a characteristic differential scanning calorimetric thermogram of Form I
Fig 2 is a characteristic differential scanning calorimetric thermogram of Form II
Fig 3 is a characteristic differential scanning calorimetric thermogram of Form III
25 Fig 4 is a characteristic differential scanning calorimetric thermogram of Form IV
Fig 5 is a characteristic X-ray diffraction pattern of Form I
Fig 6 is a characteristic X-ray diffraction pattern of Form II
Fig 7 is a characteristic X-ray diffraction pattern of Form III
Fig 8 is a characteristic X-ray diffraction pattern of Form IV
30 Fig 9 is the multi-plot of X-ray diffraction patterns of Forms I, II, III and IV
Fig 10 is a characteristic infrared absorption spectrum of Form I in potassium bromide.

Fig 11 is a characteristic infrared absorption spectrum of Form II in potassium

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bromide.

Fig 12 is a characteristic infrared absorption spectrum of Form III in potassium bromide.

Fig 13 is a characteristic infrared absorption spectrum of Form IV in potassium
5 bromide.

Detailed Description of the Invention

According to a feature of the present invention, there is provided a novel polymorphic Form-I of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl] thiazolidine-2, 4-dione maleate, and its stereoisomers having the formula I which is
10 characterized by the following data:

DSC endotherm at 100.53°C (on set at 88.65°C) (Fig. 1).

X Ray powder diffraction (2 θ) : 10.90, 14.54, 15.96, 18.46, 18.60, 19.76, 20.72, 21.84, 22.36, 22.46, 23.90, 24.04, 24.72, 25.30, 25.98, 27.44, 29.70 (Fig. 5).

IR (cm⁻¹) : 3435 (m), 2997 (w), 2773 (m), 1750 (m), 1701 (s), 1620 (m), 1510
15 (m), 1362 (m), 1332 (m), 1237 (s), 1165 (m), 864 (s), 764 (s), 717 (m), 654 (m), 540 (w),
Fig. (10).

According to another feature of the present invention, there is provided a novel polymorphic Form-II of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl] thiazolidine-2,4-dione maleate, and its stereoisomers having the formula I which is
20 characterized by the following data:

DSC : Endotherm at 127.67°C (on set at 123.17°C) Fig. 2.

XRD (2 θ): 8.90, 15.40, 18.06, 19.20, 22.30, 23.40, 23.62, 24.80, 25.10, 25.84, 26.72, 27.18, 29.30, 29.54, 29.84, 33.26 (Fig. 6).

IR : 3424 (w), 3040 (w), 2947 (m), 2720 (m), 1751 (m), 1702 (s), 1641 (m), 1618
25 (m), 1574 (w), 1541 (w), 1412 (w), 1382 (w), 1359 (m), 1326 (m), 1265 (w), 1242 (s),
1213 (w), 1162 (s), 1067 (w), 1031 (w), 865 (s), 773 (s), 713 (s), 667 (m), 576 (w), 539
(m), (Fig. 11).

According to yet another feature of the present invention, there is provided a novel polymorphic Form-III of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino] ethoxy]benzyl] thiazolidine-2,4-dione maleate and its stereoisomers having the formula I which is
30 characterized by the following data:

DSC : Endotherm at 126.41°C (on set at 122.06°C) (Fig. 3).

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XRD (2 θ): 4.60, 8.46, 9.24, 14.98, 15.86, 17.02, 18.60, 21.92, 23.50, 25.00, 25.44, 26.00, 26.38, 28.34, 33.90 (Fig. 7).

IR : 3429 (m), 2949 (m), 2738 (m), 1747 (w), 1704 (s), 1641 (m), 1617 (m), 1513 (s), 1464 (m), 1352 (m), 1244 (s), 1178 (s), 1069 (m), 862 (w), 777 (s), 717 (m), 657 (m), 589 (w) (Fig. 12).

According to yet another feature of the present invention, there is provided a novel polymorphic Form-IV of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, and its stereoisomers having the formula I which is characterized by the following data:

DSC : Endotherm at 125.39°C (on set at 121.03°C) (Fig. 4).

XRD (2 θ): 7.4, 8.8, 9.54, 14.98, 15.32, 15.82, 16.90, 17.70, 18.40, 18.54, 19.08, 19.72, 20.22, 20.48, 21.36, 21.66, 22.18, 22.58, 23.32, 23.96, 24.52, 25.38, 26.48, 27.00, 27.58, 27.94, 28.34, 28.54, 28.84, 29.10, 29.86, 30.02, 30.40, 30.52, 30.84, 31.40, 31.94 (Fig. 8).

IR : 3433 (m), 2930 (m), 1753 (w), 1705 (s), 1642 (w), 1617 (m), 1512 (s), 1467 (w), 1351 (m), 1244 (m), 1162 (m), 1061 (w), 864 (s), 765 (s), 714 (w), 658 (m), 526 (w) (Fig. 13).

According to another feature of the present invention, there is provided a process for the preparation of novel polymorphic Form-I of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, of the formula I, having the characteristics described earlier, which comprises:

- (i) synthesizing 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, employing known methods and dissolving in ethanol,
- (ii) heating the solution in a steam bath till the solid completely dissolved,
- (iii) filtering the clear solution and cooling to room temperature over a period of 18 h,
- (iv) isolating the Form I of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate formed.

According to another feature of the present invention, there is provided a process for the preparation of novel polymorphic Form-II of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, of the formula I, having the characteristics described earlier, which comprises:

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- (i) synthesizing 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, employing known methods and dissolving in acetone,
- (ii) heating the solution in a steam bath till the solid completely dissolved,
- (iii) filtering the clear solution and cooling to room temperature over a period
5 of 18 h,
- (iv) isolating the Form II of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate formed.

According to another feature of the present invention, there is provided a process for the preparation of novel polymorphic Form-III of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino] ethoxy]benzyl]thiazolidine-2,4-dione maleate, of the formula I, having the
10 characteristics described earlier, which comprises:

- (i) synthesizing 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine- 2,4-dione maleate, employing known methods and dissolving in methanol,
- (ii) heating the solution in a steam bath till the solid completely dissolved,
- (iii) filtering the clear solution and cooling to room temperature over a period
15 of 18 h,
- (iv) isolating the Form III of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate formed.

According to yet another feature of the present invention, there is provided a process for the preparation of novel polymorphic Form-IV of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino] ethoxy]benzyl]thiazolidine-2,4-dione maleate of the formula I, having the
20 characteristics described earlier, which comprises:

- (i) synthesizing 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, employing known methods and dissolving in 1,4-dioxane,
- (ii) heating the solution in a steam bath till the solid completely dissolved,
- (iii) filtering the clean solution and cooling to room temperature over a period
25 of 18 h,
- (iv) isolating the Form IV of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate formed.

30 The stereoisomers of the compounds forming part of this invention may be prepared by using reactants in their single enantiomeric form in the process wherever possible or by conducting the reaction in the presence of reagents or catalysts in their

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single enantiomer form or by resolving the mixture of stereoisomers by conventional methods. Some of the preferred methods include use of microbial resolution, resolving the diastereomeric salts formed with chiral acids such as mandelic acid, camphorsulfonic acid, tartaric acid, lactic acid, and the like wherever applicable or chiral bases such as brucine, cinchona alkaloids and their derivatives and the like. Commonly used methods are compiled by Jaques et al in "Enantiomers, Racemates and Resolution" (Wiley Interscience, 1981. Conventional reaction conditions may be employed to convert acid into an amide; the diastereomers may be separated either by fractional crystallization or chromatography and the stereoisomers of compound of formula (I) may be prepared by hydrolyzing the pure diastereomeric amide.

The present invention also envisages a pharmaceutical composition comprising any of the polymorphic Forms I to IV of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl] thiazolidine-2,4-dione maleate, of the formula (I) and a pharmaceutically acceptable carrier .

The present invention also envisages a pharmaceutical composition comprising a mixture of any of polymorphic Forms I to IV of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl] thiazolidine-2,4-dione maleate, of the formula (I) and a pharmaceutically acceptable carrier .

The pharmaceutical composition may be in the forms normally employed, such as tablets, capsules, powders, syrups, solutions, suspensions and the like, may contain flavourants, sweeteners etc. in suitable solid or liquid carriers or diluents, or in suitable sterile media to form injectable solutions or suspensions. Such compositions typically contain from 1 to 25%, preferably 1 to 15% by weight of active ingredient, the remainder of the composition being pharmaceutically acceptable carriers, diluents or solvents.

The polymorphic forms of the formula (I) as defined above are clinically administered to mammals, including man, via either oral, nasal, pulmonary, transdermal or parenteral, rectal, depot, subcutaneous, intravenous, intraurethral, intramuscular, intranasal, ophthalmic solution or an ointment. Administration by the oral route is preferred, being more convenient and avoiding the possible pain and irritation of injection. However, in circumstances where the patient cannot swallow the medication, or absorption following oral administration is impaired, as by disease or other abnormality, it is essential that the drug be administered parenterally. By either route, the dosage is in the range of about 0.01 to about 100 mg/kg body weight of the subject per

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day or preferably about 0.01 to about 30 mg/kg body weight per day administered singly or as a divided dose. However, the optimum dosage for the individual subject being treated will be determined by the person responsible for treatment, generally smaller doses being administered initially and thereafter increments made to determine the most
5 suitable dosage.

Suitable pharmaceutically acceptable carriers include solid fillers or diluents and sterile aqueous or organic solutions. The active ingredient will be present in such pharmaceutical compositions in the amounts sufficient to provide the desired dosage in the range as described above. Thus, for oral administration, the polymorphic form can be
10 combined with a suitable solid or liquid carrier or diluent to form capsules, tablets, powders, syrups, solutions, suspensions and the like. The pharmaceutical compositions, may, if desired, contain additional components such as flavourants, sweeteners, excipients and the like. For parenteral administration, the polymorphic form can be combined with sterile aqueous or organic media to form injectable solutions or suspensions. For
15 example, solutions in sesame or peanut oil, aqueous propylene glycol and the like can be used, as well as aqueous solutions of water-soluble pharmaceutically-acceptable acid addition salts or salts with base of the compounds. Aqueous solutions with the active ingredient dissolved in polyhydroxylated castor oil may also be used for injectable solutions. The injectable solutions prepared in this manner can then be administered
20 intravenously, intraperitoneally, subcutaneously, or intramuscularly, with intramuscular administration being preferred in humans.

For nasal administration, the preparation may contain the polymorphic forms of the present invention dissolved or suspended in a liquid carrier, in particular an aqueous carrier, for aerosol application. The carrier may contain additives such as solubilizing
25 agents, such as propylene glycol, surfactants, absorption enhancers such as lecithin (phosphatidylcholine) or cyclodextrin or preservatives such as parabenes.

Tablets, dragees or capsules having talc and/or a carbohydrate carrier binder or the like are particularly suitable for any oral application. Preferably, carriers for tablets, dragees or capsules include lactose, corn starch and/or potato starch. A syrup or elixir
30 can be used in cases where a sweetened vehicle can be employed.

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A typical tablet production method is exemplified below:

Tablet Production Example:

	a) 1) Active ingredient	30 g
	2) Lactose	95 g
5	3) Corn starch	30 g
	4) Carboxymethyl cellulose	44 g
	5) Magnesium stearate	1 g

200 g for 1000 tablets

10 The ingredients 1 to 3 are uniformly blended with water and granulated after drying under reduced pressure. The ingredient 4 and 5 are mixed well with the granules and compressed by a tableting machine to prepare 1000 tablets each containing 30 mg of active ingredient.

	b) 1) Active ingredient	30 g
15	2) Calcium phosphate	90 g
	3) Lactose	40 g
	4) Corn starch	35 g
	5) Polyvinyl pyrrolidone	3.5 g
	6) Magnesium stearate	1.5 g

200 g for 1000 tablets

20 The ingredients 1-4 are uniformly moistened with an aqueous solution of 5 and granulated after drying under reduced pressure. Ingredient 6 is added and granules are compressed by a tableting machine to prepare 1000 tablets containing 30 mg of
25 ingredient 1.

The present invention is described in detail in the examples given below which are provided by way of illustration only and therefore should not be construed to limit the scope of the invention.

EXAMPLES

Example-1

30 A mixture of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione (69 g, 0.19 M) and maleic acid (22.8 g, 0.19 M) was heated under reflux while stirring in iso-propanol (1.0 L) until a clear solution was obtained (1-2 h). The reaction

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mass was allowed to cool to RT while stirring for 15-20 h. The white to off-white crystalline compound was filtered, washed with iso-propanol (3 x 100 ml) and pet. ether (2 x 100 ml) dried to furnish white to off-white product (84.5 g; Yield : 92%).

Example – 2

5 1 g of the 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate obtained by the process as described in Example-1 was taken in 10 ml EtOH and heated on a steam bath till the solid completely dissolved. The clear solution was allowed to cool to RT over a period of 18 h to yield 80% of >99% pure polymorphic Form I of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate.

Example – 3

15 1 g of the 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate obtained by the process as described in Example-1 was taken in 50 ml acetone and heated on a steam bath till the solid completely dissolved. The solution was allowed to cool to RT over a period of 18 h to yield 60% of > 99% pure polymorphic Form II of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate.

Example – 4

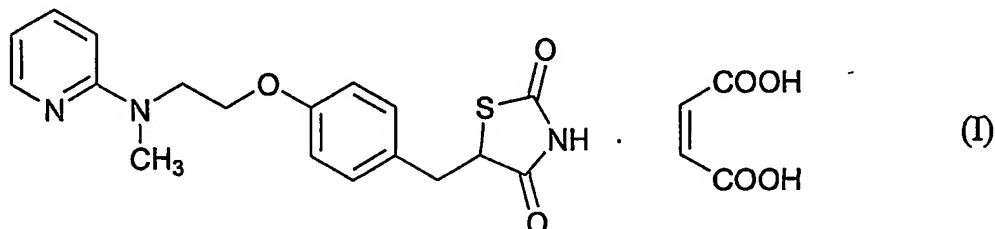
20 1 g of the 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate obtained by the process as described in Example-1 was dissolved in 10 ml of methanol and heated on a steam bath till the solid completely dissolved. The clear solution was filtered and allowed to cool to RT over a period of 18 h to yield 75% of > 99% pure polymorphic Form III of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl] thiazolidine-2,4-dione maleate.

Example – 5

25 1 g of the 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate obtained by the process as described in Example-1 was taken in 10 ml 1,4-dioxane and heated on a steam bath till the solid completely dissolved. The clear solution was allowed to cool to RT over a period of 18 h to yield 70% of > 99% pure polymorphic Form IV of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate.

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CLAIMS

1. A novel polymorphic Form-I of 5-[4-[2-[N-methyl-N-(2-pyridyl) amino] ethoxy]benzyl]thiazolidine-2,4-dione maleate, and its stereoisomers having the formula I



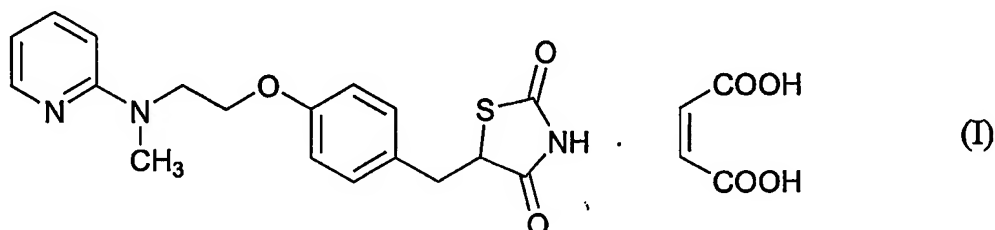
- 5 which is characterized by the following data:

DSC endotherm at 100.53°C (on set at 88.65°C),

X Ray powder diffraction (2 θ) : 10.90, 14.54, 15.96, 18.46, 18.60, 19.76, 20.72, 21.84, 22.36, 22.46, 23.90, 24.04, 24.72, 25.30, 25.98, 27.44, 29.70,

IR (cm⁻¹) : 3435 (m), 2997 (w), 2773 (m), 1750 (m), 1701 (s), 1620 (m), 1510 (m), 1362 (m), 1332 (m), 1237 (s), 1165 (m), 864 (s), 764 (s), 717 (m), 654 (m), 540 (w).

2. A novel polymorphic Form-II of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino] ethoxy]benzyl]thiazolidine-2,4-dione maleate, and its stereoisomers having the formula I



which is characterized by the following data:

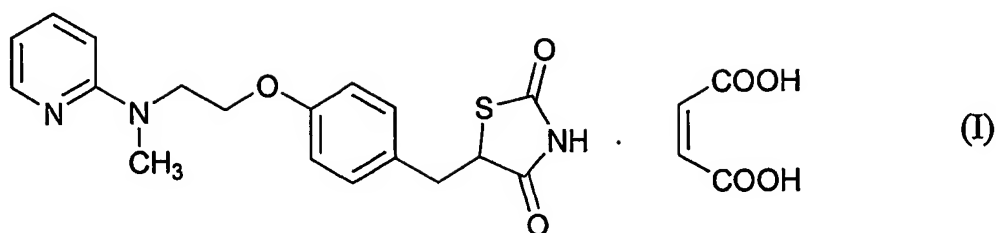
15 DSC : Endotherm at 127.67°C (on set at 123.17°C),

XRD (2 θ): 8.90, 15.40, 18.06, 19.20, 22.30, 23.40, 23.62, 24.80, 25.10, 25.84, 26.72, 27.18, 29.30, 29.54, 29.84, 33.26,

IR : 3424 (w), 3040 (w), 2947 (m), 2720 (m), 1751 (m), 1702 (s), 1641 (m), 1618 (m), 1574 (w), 1541 (w), 1412 (w), 1382 (w), 1359 (m), 1326 (m), 1265 (w), 1242 (s), 1213 (w), 1162 (s), 1067 (w), 1031 (w), 865 (s), 773 (s), 713 (s), 667 (m), 576 (w), 539 (m).

3. A novel polymorphic Form-III of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino] ethoxy]benzyl]thiazolidine-2,4-dione maleate and its stereoisomers having the formula I

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which is characterized by the following data:

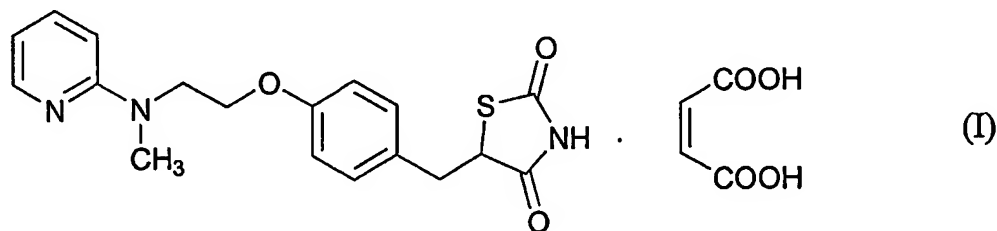
DSC : Endotherm at 126.41°C (on set at 122.06°C),

XRD (2 θ): 4.60, 8.46, 9.24, 14.98, 15.86, 17.02, 18.60, 21.92, 23.50, 25.00,

5 25.44, 26.00, 26.38, 28.34, 33.90,

IR : 3429 (m), 2949 (m), 2738 (m), 1747 (w), 1704 (s), 1641 (m), 1617 (m), 1513 (s), 1464 (m), 1352 (m), 1244 (s), 1178 (s), 1069 (m), 862 (w), 777 (s), 717 (m), 657 (m), 589 (w).

4. A novel polymorphic Form-IV of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, and its stereoisomers having the formula I



which is characterized by the following data:

DSC : Endotherm at 125.39°C (on set at 121.03°C),

XRD (2 θ): 7.4, 8.8, 9.54, 14.98, 15.32, 15.82, 16.90, 17.70, 18.40, 18.54, 19.08, 19.72, 20.22, 20.48, 21.36, 21.66, 22.18, 22.58, 23.32, 23.96, 24.52, 25.38, 26.48, 27.00, 27.58, 27.94, 28.34, 28.54, 28.84, 29.10, 29.86, 30.02, 30.40, 30.52, 30.84, 31.40, 31.94,

IR : 3433 (m), 2930 (m), 1753 (w), 1705 (s), 1642 (w), 1617 (m), 1512 (s), 1467 (w), 1351 (m), 1244 (m), 1162 (m), 1061 (w), 864 (s), 765 (s), 714 (w), 658 (m), 526 (w).

5. A process for the preparation of novel polymorphic Form I of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, which comprises

- (i) synthesizing 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, employing known methods and dissolving in ethanol,
 - (ii) heating the solution in a steam bath till the solid completely dissolved,
 - (iii) filtering the clean solution and cooling to room temperature over a period
- 25 of 18 h and

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(iv) isolating the Form I of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate formed.

6. A process for the preparation of novel polymorphic Form II of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, which comprises:

- 5 (i) synthesizing 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, employing known methods and dissolving in acetone,
(ii) heating the solution in a steam bath till the solid completely dissolved,
(iii) filtering the clean solution and cooling to room temperature over a period of 18 h and

- 10 (iv) isolating the Form II of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate formed.

7. A process for the preparation of novel polymorphic Form III of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, which comprises:

- 15 (i) synthesizing 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, employing known methods and dissolving in methanol,
(ii) heating the solution in a steam bath till the solid completely dissolved,
(iii) filtering the clean solution and cooling to room temperature over a period of 18 h and

- 20 (iv) isolating the Form III of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate formed.

8. A process for the preparation of novel polymorphic Form IV of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, which comprises:

- 25 (i) synthesizing 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, employing known methods and dissolving in 1,4-dioxane,
(ii) heating the solution in a steam bath till the solid completely dissolved,
(iii) filtering the clean solution and cooling to room temperature over a period of 18 h and

- 30 (iv) isolating the Form IV of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate formed.

9. A pharmaceutical composition comprising a mixture of any of polymorphic Forms

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I to IV of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl] thiazolidine-2,4-dione maleate, of the formula (I) and a pharmaceutically acceptable carrier, diluent, excipient or solvate.

10. A pharmaceutical composition as claimed in claim 9, in the form of a tablet,
5 capsule, powder, syrup, solution or suspension.
11. A method of preventing or treating hyperlipemia, hypercholesteremia, hyperglycemia, osteoporosis, obesity, glucose intolerance, leptin resistance, insulin resistance, or diseases in which insulin resistance is the underlying pathophysiological mechanism comprising administering a polymorphic Form selected from Form I to IV of
10 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, having the formula I as defined in claims 1-4 or a pharmaceutical composition as claimed in claims 9 and 10 to a patient in need thereof.
12. A method according to claim 11, wherein the disease is type II diabetes, impaired glucose tolerance, dyslipidaemia, disorders related to Syndrome X such as hypertension,
15 obesity, atherosclerosis, hyperlipidemia, coronary artery disease and other cardiovascular disorders, certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, retinopathy, nephropathy, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), useful as aldose reductase inhibitors, for improving cognitive functions in dementia and
20 treating diabetic complications, osteoporosis, inflammatory bowel diseases, myotonic dystrophy, pancreatitis, arteriosclerosis, xanthoma and cancer.
13. A method of reducing plasma glucose, triglycerides, total cholesterol, LDL, VLDL and free fatty acids in the plasma comprising administering a polymorphic Form selected from Form I to IV of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]
25 thiazolidine-2,4-dione maleate, having the formula I as defined in claims 1-4 or a pharmaceutical composition as claimed in claims 9 and 10.
14. A method of preventing or treating hyperlipemia, hypercholesteremia, hyperglycemia, osteoporosis, obesity, glucose intolerance, leptin resistance, insulin resistance, or diseases in which insulin resistance is the underlying pathophysiological
30 mechanism comprising administering a polymorphic Form selected from Form I to IV of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, having the formula I as defined in claims 1-4 or a pharmaceutical composition as claimed

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in claims 9 and 10 in combination / concomittant with HMG CoA reductase inhibitors or fibrates or nicotinic acid or cholestyramine or colestipol or probucol which may be administered together or within such a period as to act synergistically together to a patient in need thereof.

- 5 15. A method according to claim 14, wherein the disease is type II diabetes, impaired glucose tolerance, dyslipidaemia, disorders related to Syndrome X such as hypertension, obesity, atherosclerosis, hyperlipidemia, coronary artery disease and other cardiovascular disorders, certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, retinopathy, nephropathy, disorders
10 related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), useful as aldose reductase inhibitors, for improving cognitive functions in dementia and treating diabetic complications, osteoporosis, inflammatory bowel diseases, myotonic dystrophy, pancreatitis, arteriosclerosis, xanthoma and cancer.
16. A method according to claim 14 for the treatment and / or prophylaxis of disorders
15 related to Syndrome X, which comprises administering a polymorphic Form selected from Form I to IV of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl] thiazolidine-2,4-dione maleate, having the formula I as defined in claims 1-4 in combination with HMG CoA reductase inhibitors or fibrates or nicotinic acid or cholestyramine or colestipol or probucol which may be administered together or within such a period as to
20 act synergistically together.
17. A method of reducing plasma glucose, triglycerides, total cholesterol, LDL, VLDL and free fatty acids in the plasma, which comprises administering a polymorphic Form selected from Form I to IV of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy] benzyl]thiazolidine-2,4-dione maleate, having the formula I as defined in claims 1-4 or a
25 pharmaceutical composition as claimed in claims 9 and 10 in combination / concomittant with HMG CoA reductase inhibitors or fibrates or nicotinic acid or cholestyramine or colestipol or probucol which may be administered together or within such a period as to act synergistically together to a patient in need thereof.
18. Use of a polymorphic Form selected from Form I to IV of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, having the formula I as
30 defined in claims 1-4 or a pharmaceutical composition as claimed in claims 9 and 10 for preventing or treating hyperlipidemia, hypercholesteremia, hyperglycemia, osteoporosis,

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obesity, glucose intolerance, leptin resistance, insulin resistance, or diseases in which insulin resistance is the underlying pathophysiological mechanism.

19. Use of a polymorphic Form according to claim 18, wherein the disease is type II diabetes, impaired glucose tolerance, dyslipidaemia, disorders related to Syndrome X
5 such as hypertension, obesity, atherosclerosis, hyperlipidemia, coronary artery disease and other cardiovascular disorders, certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, retinopathy, nephropathy, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), useful as aldose reductase inhibitors, for improving cognitive
10 functions in dementia and treating diabetic complications, osteoporosis, inflammatory bowel diseases, myotonic dystrophy, pancreatitis, arteriosclerosis, xanthoma or cancer.
20. Use of a polymorphic Form selected from Form I to IV of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, having the formula I as defined in claims 1-4 or a pharmaceutical composition as claimed in claims 9 and 10 for
15 reducing plasma glucose, triglycerides, total cholesterol, LDL, VLDL and free fatty acids in the plasma.
21. Use of a polymorphic Form selected from Form I to IV of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, having the formula I as defined in claims 1-4 or a pharmaceutical composition as claimed in claims 9 and 10 in
20 combination/ concomittant with HMG CoA reductase inhibitors, fibrates, nicotinic acid, cholestyramine, colestipol or probucol which may be administered together or within such a period as to act synergistically together for preventing or treating hyperlipidemia, hypercholesteremia, hyperglycemia, osteoporosis, obesity, glucose intolerance, leptin resistance, insulin resistance, or diseases in which insulin resistance is the underlying
25 pathophysiological mechanism to a patient in need thereof.
22. Use of a polymorphic Form according to claim 21, wherein the disease is type II diabetes, impaired glucose tolerance, dyslipidaemia, disorders related to Syndrome X such as hypertension, obesity, atherosclerosis, hyperlipidemia, coronary artery disease and other cardiovascular disorders, certain renal diseases including glomerulonephritis,
30 glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, retinopathy, nephropathy, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), useful as aldose reductase inhibitors, for improving cognitive

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functions in dementia and treating diabetic complications, osteoporosis, inflammatory bowel diseases, myotonic dystrophy, pancreatitis, arteriosclerosis, xanthoma or cancer.

23. Use of a polymorphic Form selected from Form I to IV of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, having the formula I as defined in claims 1-4 or a pharmaceutical composition as claimed in claims 9 and 10 in combination/concomittant with HMG CoA reductase inhibitors, fibrates, nicotinic acid, cholestyramine, colestipol or probucol for reducing plasma glucose, triglycerides, total cholesterol, LDL, VLDL or free fatty acids in the plasma.
24. Use of a polymorphic Form selected from Form I to IV of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, having the formula I as defined in claims 1-4 or a pharmaceutical composition as claimed in claims 9 and 10 for preparing a medicament for preventing or treating hyperlipidemia, hypercholesteremia, hyperglycemia, osteoporosis, obesity, glucose intolerance, leptin resistance, insulin resistance, or diseases in which insulin resistance is the underlying pathophysiological mechanism.
25. Use of a polymorphic form according to claim 24, wherein the disease is type II diabetes, impaired glucose tolerance, dyslipidaemia, disorders related to Syndrome X such as hyper-tension, obesity, atherosclerosis, hyperlipidemia, coronary artery disease and other cardiovascular disorders, certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, retinopathy, nephropathy, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), useful as aldose reductase inhibitors, for improving cognitive functions in dementia and treating diabetic complications, osteoporosis, inflammatory bowel diseases, myotonic dystrophy, pancreatitis, arteriosclerosis, xanthoma or cancer.
26. Use of a polymorphic Form selected from Form I to IV of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, having the formula I as defined in claims 1-4 or a pharmaceutical composition as claimed in claims 9 and 10 for preparing a medicament for reducing plasma glucose, triglycerides, total cholesterol, LDL, VLDL and free fatty acids in the plasma.
27. Use of a polymorphic Form selected from Form I to IV of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, having the formula I as defined in claims 1-4 or a pharmaceutical composition as claimed in claims 9 and 10 for

- 20 -

preparing a medicament in combination/concomittant with HMG CoA reductase inhibitors, fibrates, nicotinic acid, cholestyramine, colestipol or probucol for preventing or treating hyperlipemia, hypercholesteremia, hyperglycemia, osteoporosis, obesity, glucose intolerance, leptin resistance, insulin resistance, or diseases in which insulin resistance is the underlying pathophysiological mechanism.

28. Use of a polymorphic form according to claim 27, wherein the disease is type II diabetes, impaired glucose tolerance, dyslipidaemia, disorders related to Syndrome X such as hypertension, obesity, atherosclerosis, hyperlipidemia, coronary artery disease and other cardiovascular disorders, certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, retinopathy, nephropathy, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), useful as aldose reductase inhibitors, for improving cognitive functions in dementia and treating diabetic complications, osteoporosis, inflammatory bowel diseases, myotonic dystrophy, pancreatitis, arteriosclerosis, xanthoma or cancer.

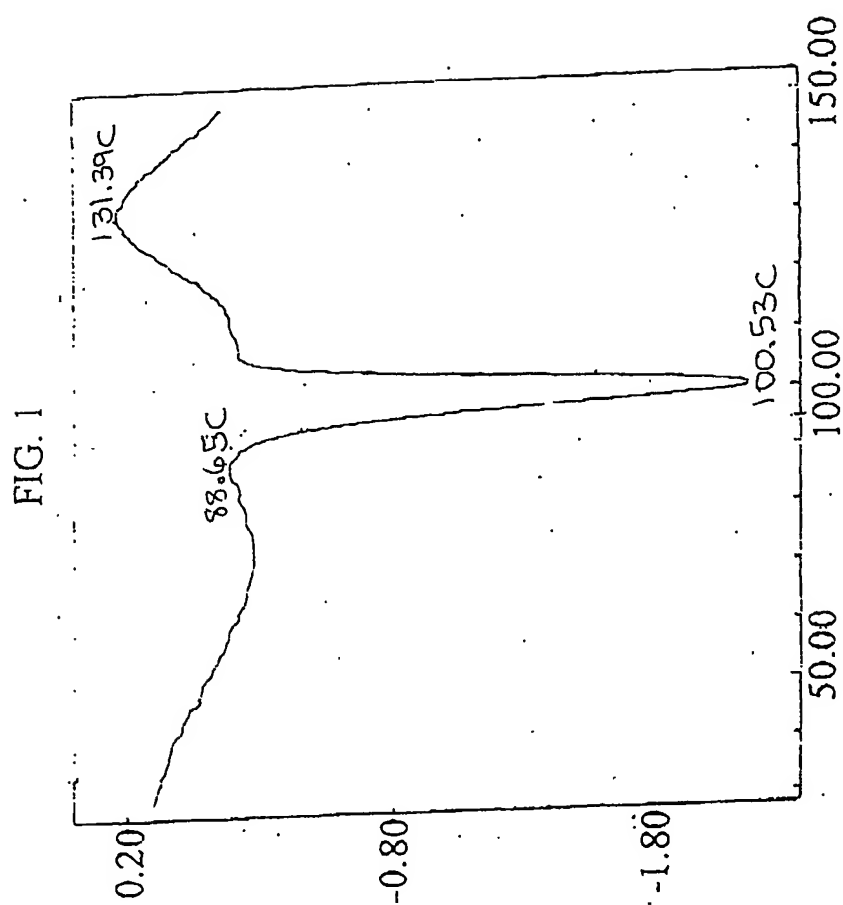
29. Use of a polymorphic Form selected from Form I to IV of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, having the formula I as defined in claims 1-4 or a pharmaceutical composition as claimed in claims 9 and 10 for preparing a medicament in combination/concomittant with HMG CoA reductase inhibitors, fibrates, nicotinic acid, cholestyramine, colestipol or probucol for reducing plasma glucose, triglycerides, total cholesterol, LDL, VLDL or free fatty acids in the plasma.

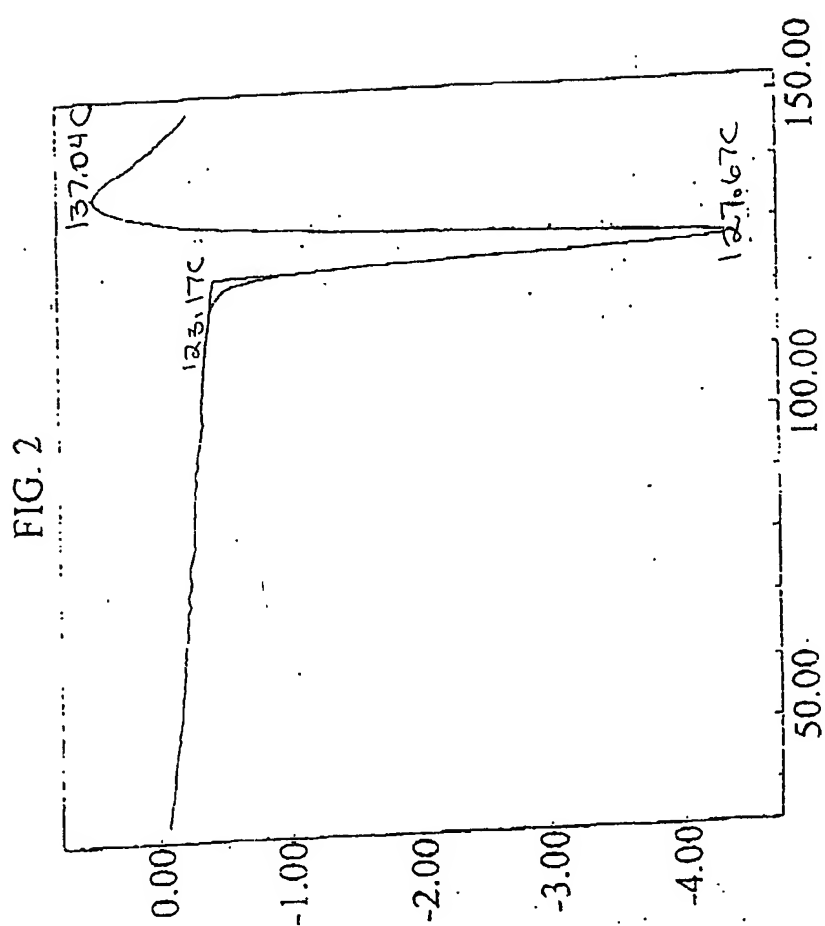
30. A medicine for preventing or treating hyperlipidemia, hypercholesteremia, hyperglycemia, osteoporosis, obesity, glucose intolerance, leptin resistance, insulin resistance, or diseases in which insulin resistance is the underlying pathophysiological mechanism comprising administering an effective amount of a polymorphic Form selected from Form I to IV of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, having the formula I as defined in claims 1-4 or a pharmaceutical composition as claimed in claims 9 and 10.

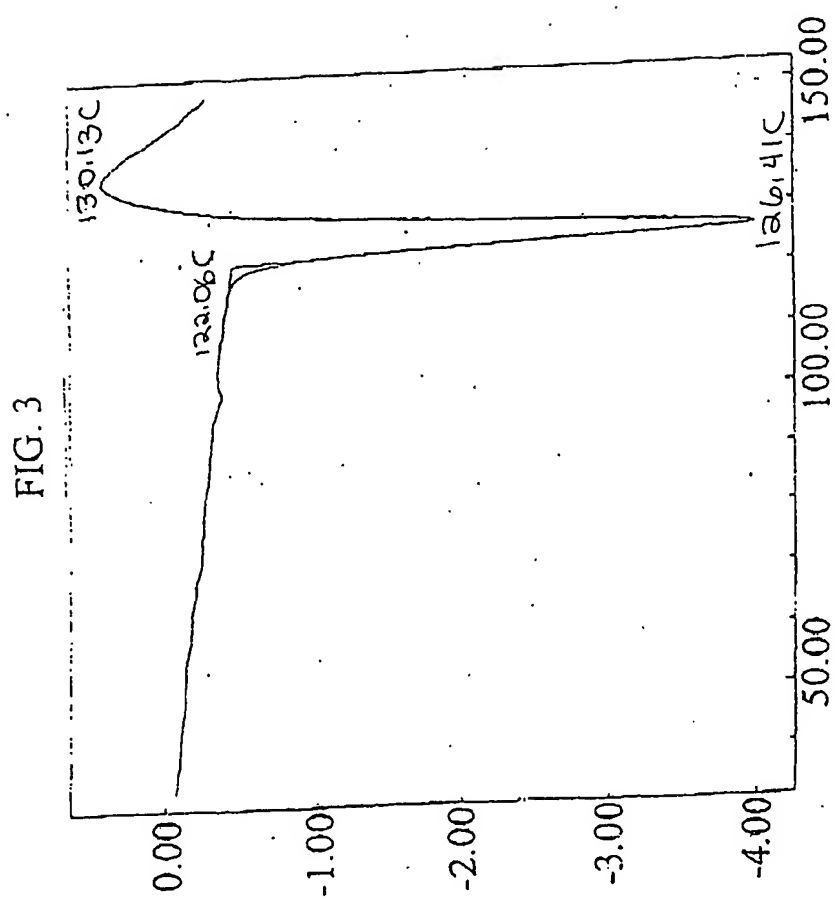
31. A medicine according to claim 30, wherein the disease is type II diabetes, impaired glucose tolerance, dyslipidaemia, disorders related to Syndrome X such as hypertension, obesity, atherosclerosis, hyperlipidemia, coronary artery disease and other cardiovascular disorders, certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, retinopathy,

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- nephropathy, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), useful as aldose reductase inhibitors, for improving cognitive functions in dementia and treating diabetic complications, osteoporosis, inflammatory bowel diseases, myotonic dystrophy, pancreatitis, arteriosclerosis, xanthoma or cancer.
- 5 32. A medicine for reducing plasma glucose, triglycerides, total cholesterol, LDL, VLDL and free fatty acids in the plasma comprising an effective amount of a polymorphic Form selected from Form I to IV of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, having the formula I as defined in claims 1-4 or a pharmaceutical composition as claimed in claims 9 and 10.
- 10 33. A medicine for preventing or treating hyperlipidemia, hypercholesteremia, hyperglycemia, osteoporosis, obesity, glucose intolerance, leptin resistance, insulin resistance, or diseases in which insulin resistance is the underlying pathophysiological mechanism comprising a polymorphic Form selected from Form I to IV of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, having the
- 15 formula I as defined in claims 1-4 or a pharmaceutical composition as claimed in claims 9 and 10 and HMG CoA reductase inhibitors, fibrates, nicotinic acid, cholestyramine, colestipol or probucol.
34. A medicine according to claim 33, wherein the disease is type II diabetes, impaired glucose tolerance, dyslipidaemia, disorders related to Syndrome X such as
- 20 hypertension, obesity, atherosclerosis, hyperlipidemia, coronary artery disease and other cardiovascular disorders, certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, retinopathy, nephropathy, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), useful as aldose reductase inhibitors, for improving cognitive
- 25 functions in dementia and treating diabetic complications, osteoporosis, inflammatory bowel diseases, myotonic dystrophy, pancreatitis, arteriosclerosis, xanthoma or cancer.
35. A medicine for reducing plasma glucose, triglycerides, total cholesterol, LDL, VLDL and free fatty acids in the plasma, which comprises a polymorphic Form selected from Form I to IV of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-
- 30 2,4-dione maleate, having the formula I as defined in claims 1-4 or a pharmaceutical composition as claimed in claims 9 and 10 and HMG CoA reductase inhibitors, fibrates, nicotinic acid, cholestyramine, colestipol or probucol.







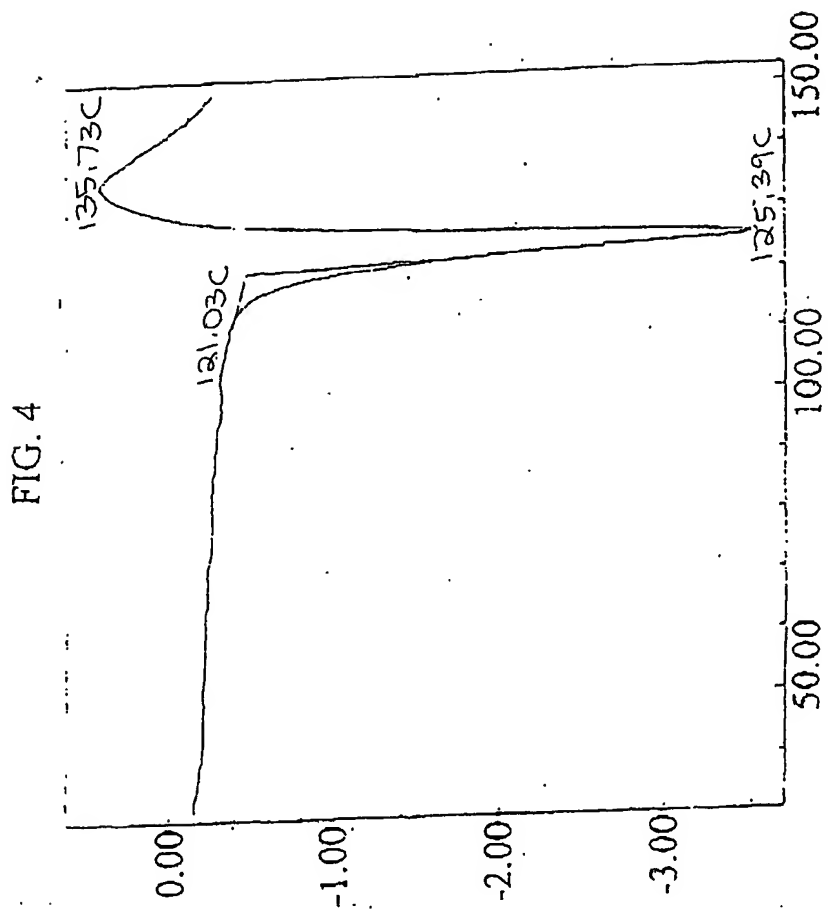


FIG. 5

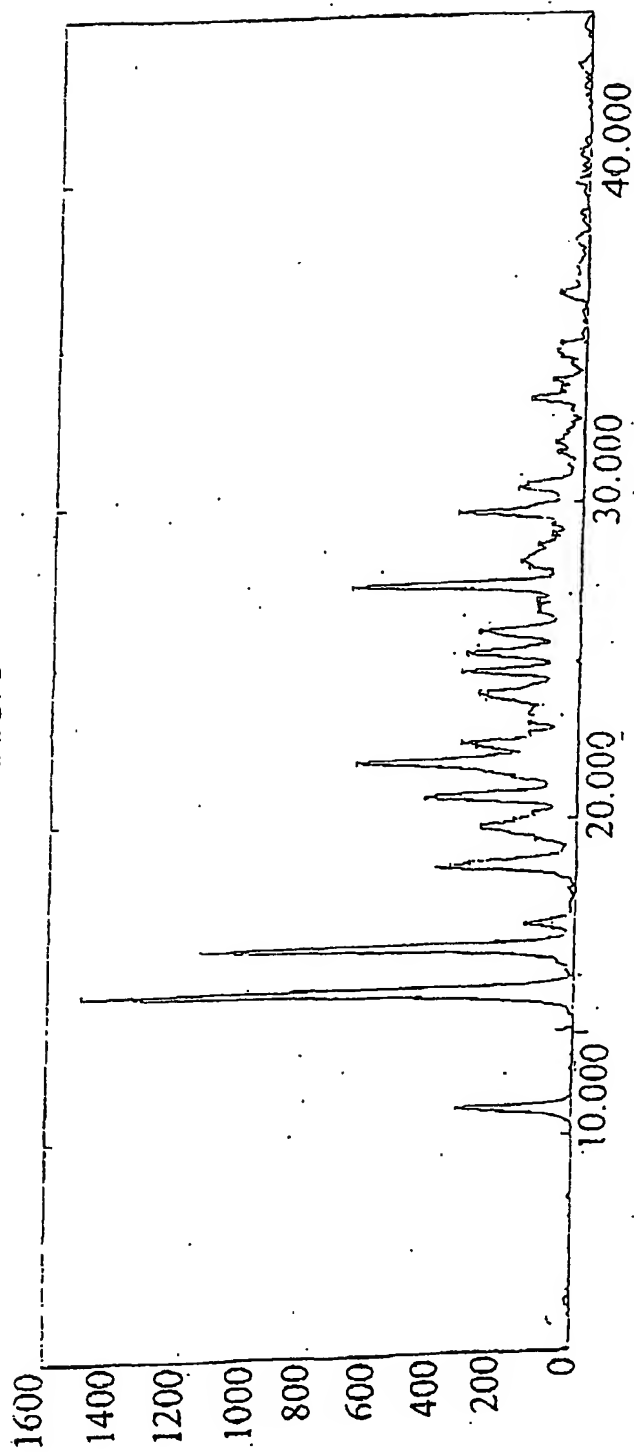


FIG. 6

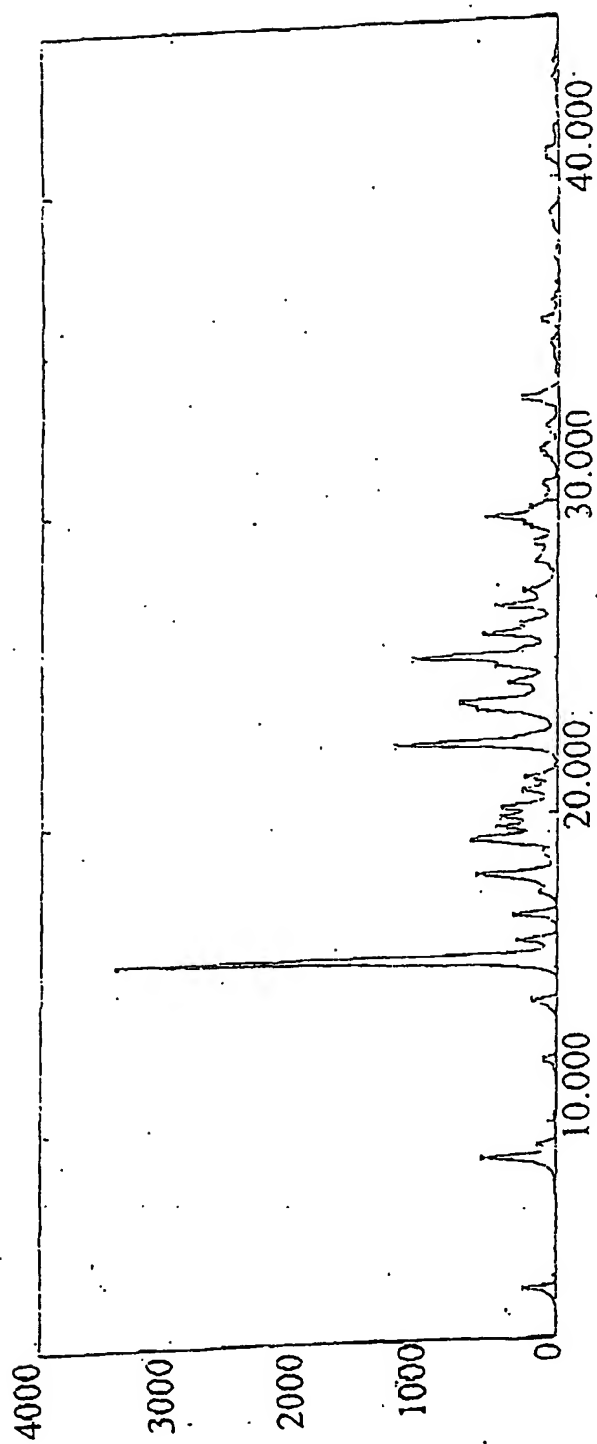


FIG. 7

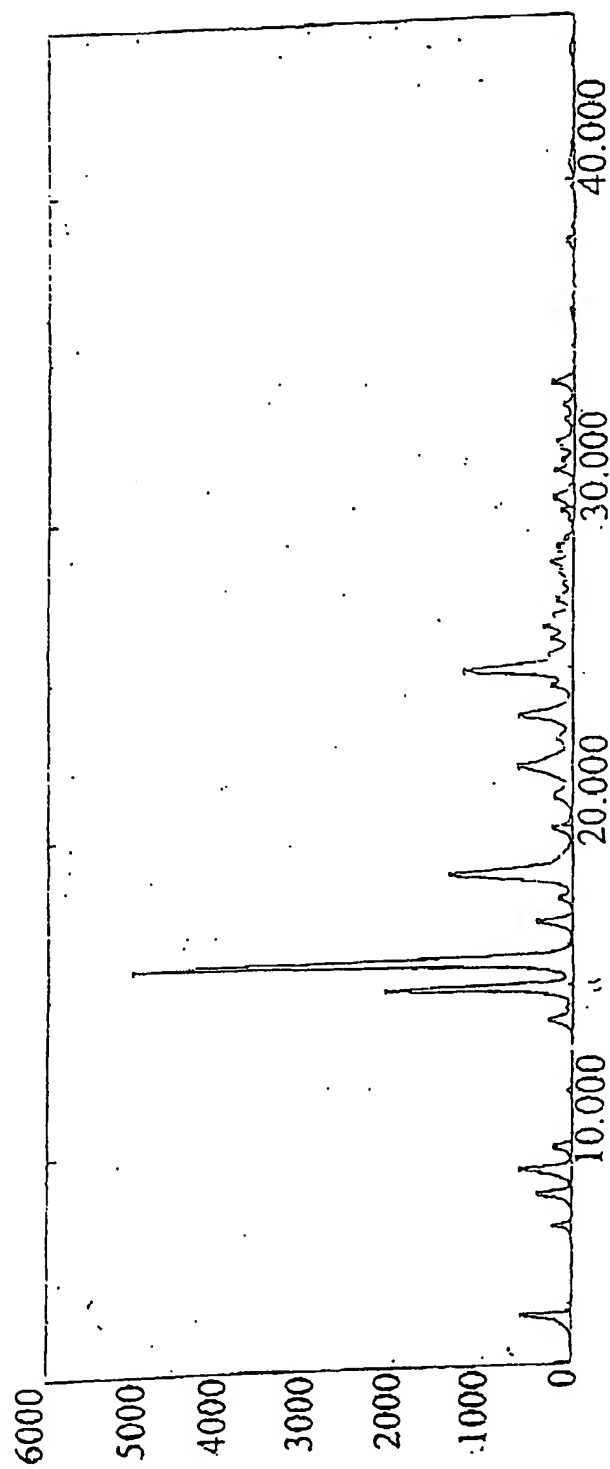


FIG. 8

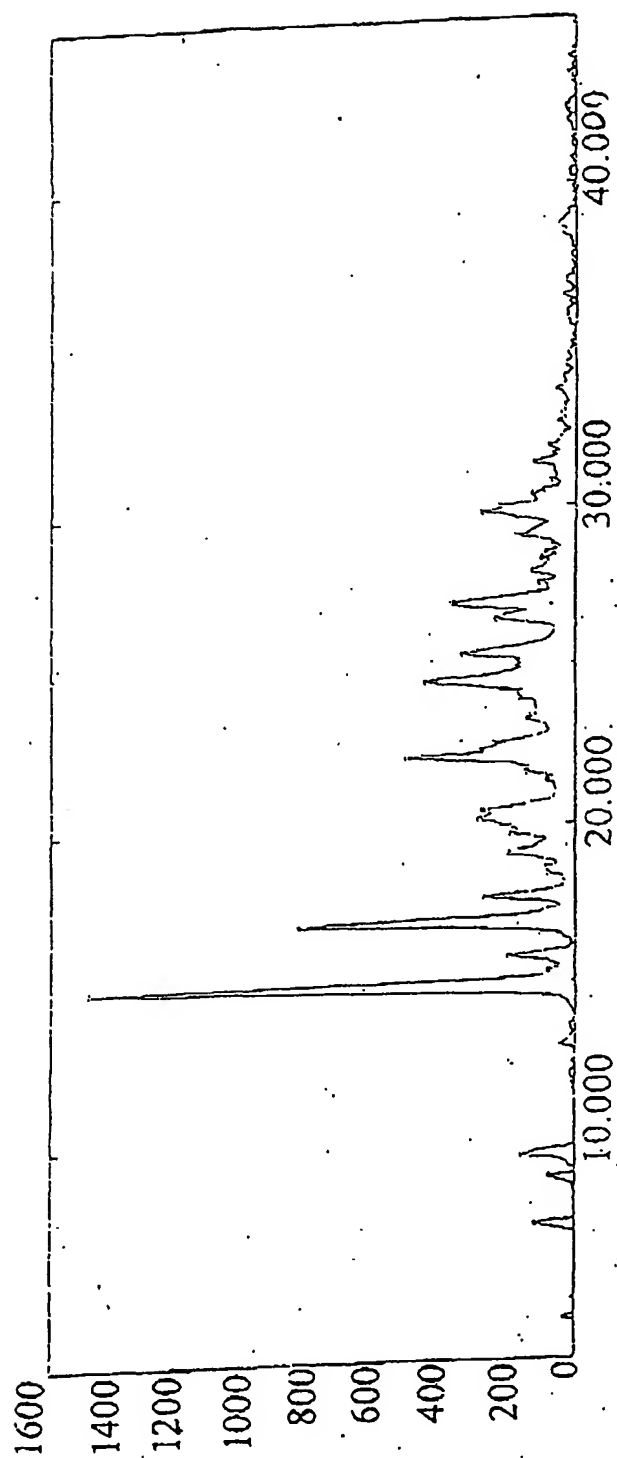


Fig. 9

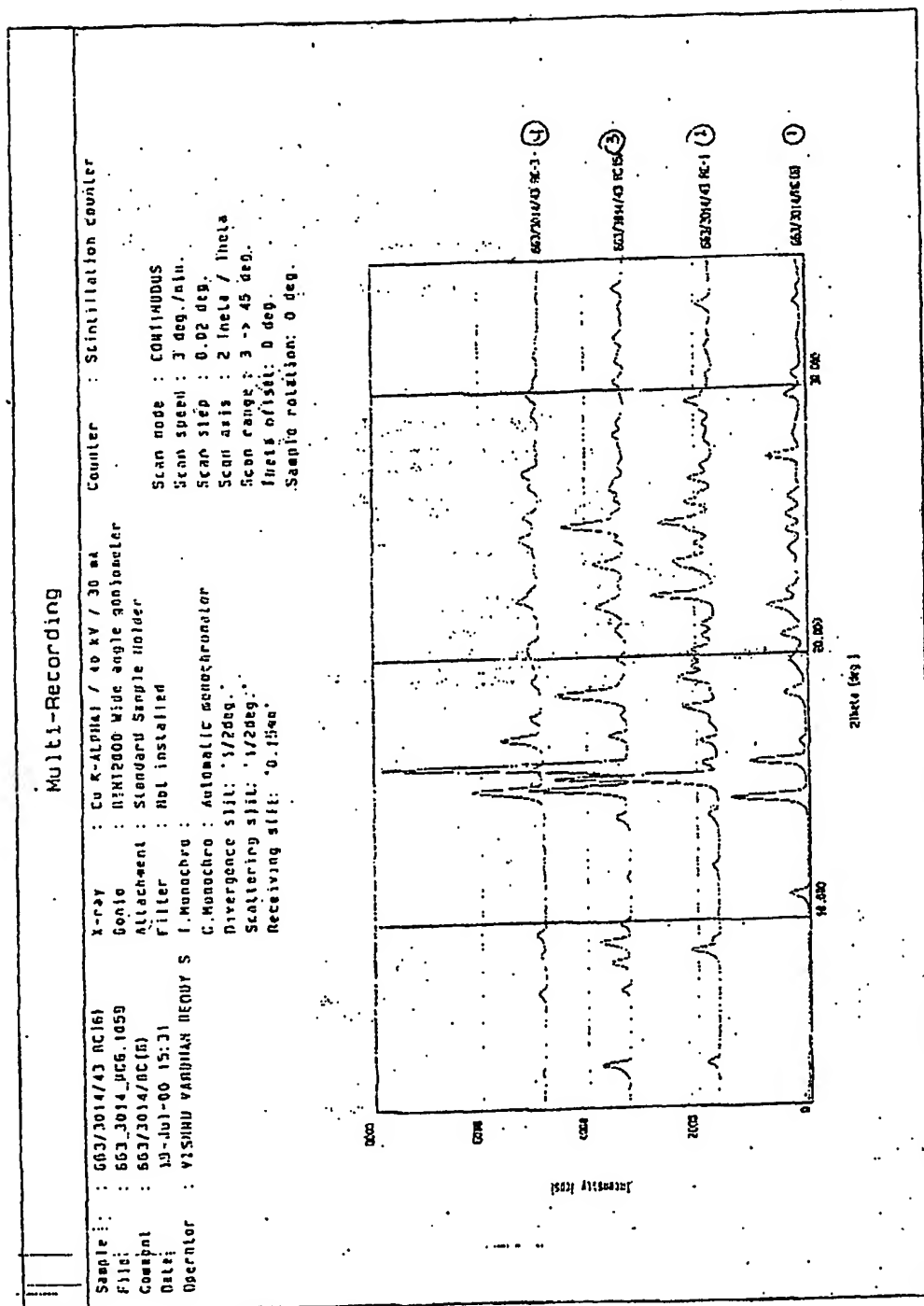


FIG. 10

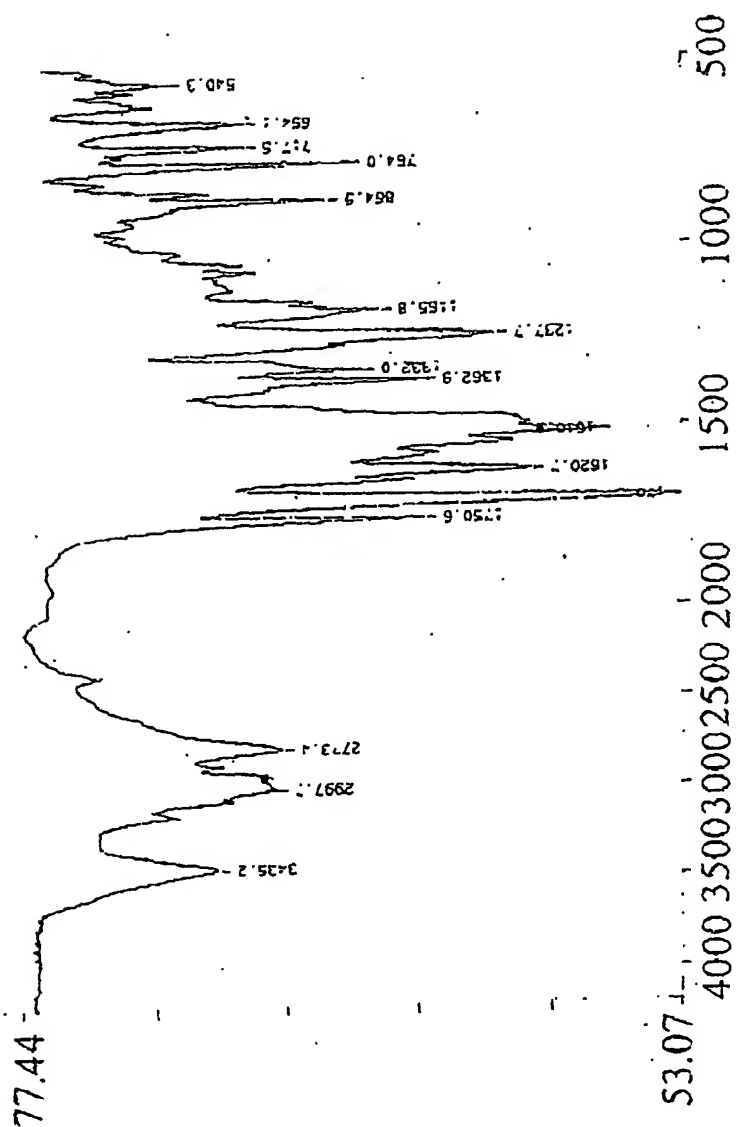


FIG. 11

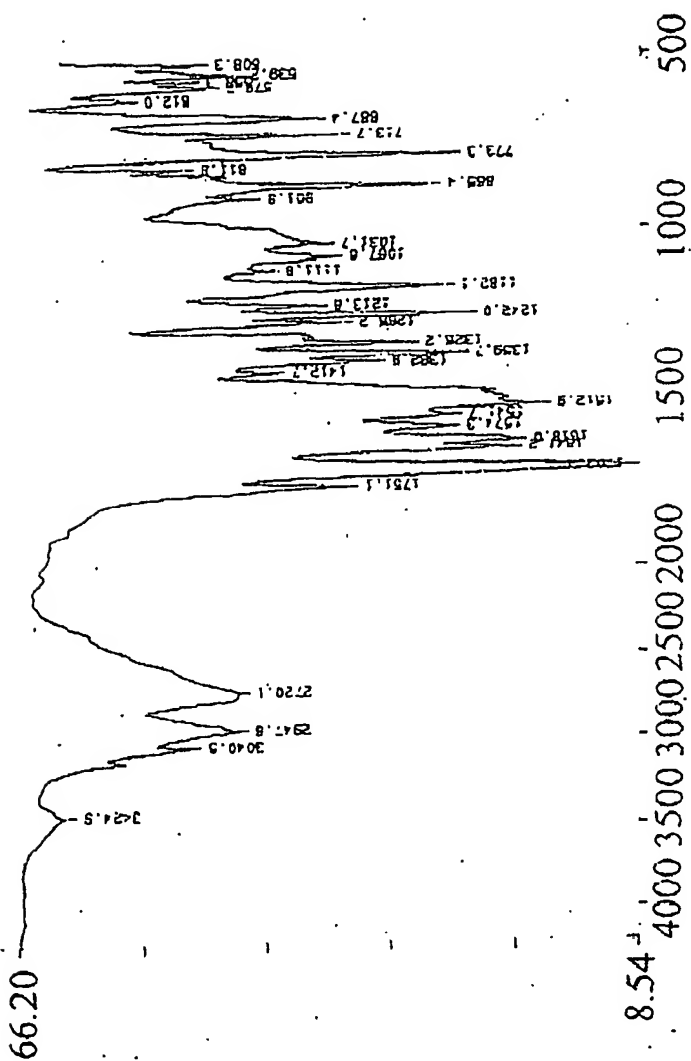


FIG. 12

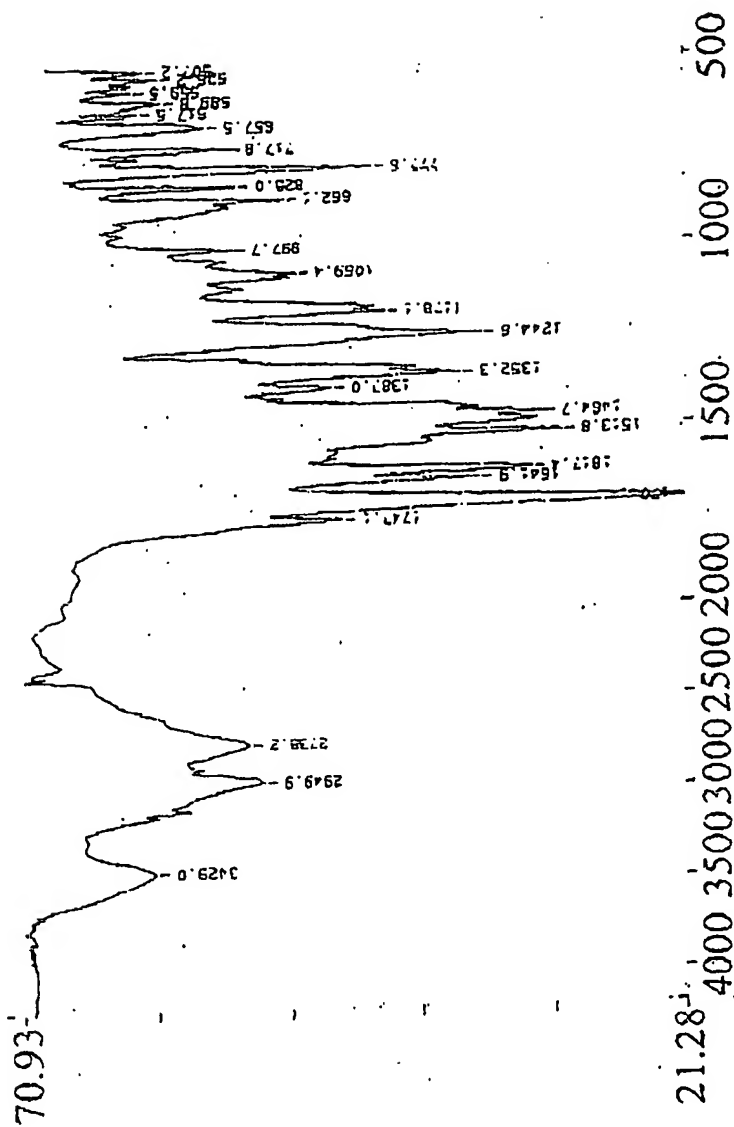
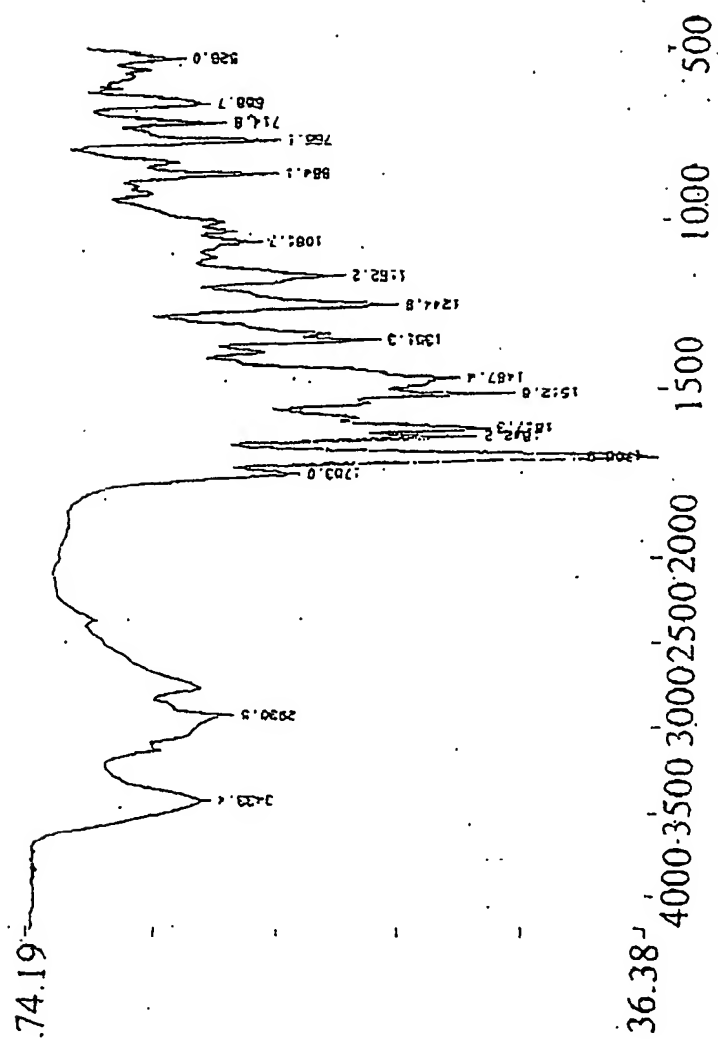


FIG. 13



INTERNATIONAL SEARCH REPORT

Inte.....al Application No

PCT/US 01/29896

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07D417/12 C07D277/34 A61K31/425 A61P3/10 A61P9/12		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07D		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	WO 00 64896 A (BLACKLER PAUL DAVID JAMES ; GILES ROBERT GORDON (GB); SMITHKLINE BE) 2 November 2000 (2000-11-02) the whole document ---	1-35
Y	WO 94 05659 A (SMITHKLINE BEECHAM PLC ; POOL COLIN RIPLEY (GB); ROMAN ROBIN SHERWO) 17 March 1994 (1994-03-17) the whole document ---	1-35
Y	WO 97 27191 A (REDDY RESEARCH FOUNDATION ; REDDY CHEMINOR INC (US)) 31 July 1997 (1997-07-31) cited in the application p.1, 1.5-35; p.3, 1.1-9; claims. --- -/--	1-35
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/29896

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 306 228 A (BEECHAM GROUP PLC) 8 March 1989 (1989-03-08) cited in the application page 38; example 30 ----	1-35
A	PARKS D,J,; TOMKINSON, N.C.O.; VILLENEUVE M.S.; BLANCHARD S.G.: "Differential activity of Rosiglitazone enantiomers at PPAR." BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 8, 1998, pages 3657-3658, XP002191825 the whole document ----	1-35
A	WO 97 41120 A (LOHRAY BRAJ BHUSHAN ; RAMANUJAM RAJAGOPALAN (IN); REDDY RESEARCH FO) 6 November 1997 (1997-11-06) p.1, 1.1 to p.2, 1.4; p.4, 1.15-1.28; p.28, 1.2-1.10; example 13 p.51; claims 15 and 29-31. -----	1-35

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/29896

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0064896 A	02-11-2000	AU 4130800 A	10-11-2000
		EP 1173435 A1	23-01-2002
		WO 0064896 A1	02-11-2000
		NO 20015147 A	17-12-2001
WO 9405659 A	17-03-1994	AP 513 A	30-07-1996
		AT 182147 T	15-07-1999
		AU 674880 B2	16-01-1997
		AU 4973093 A	29-03-1994
		BR 1100916 A3	04-07-2000
		CA 2143849 A1	17-03-1994
		CN 1101911 A ,B	26-04-1995
		CN 1183275 A ,B	03-06-1998
		CN 1183413 A ,B	03-06-1998
		CN 1183276 A ,B	03-06-1998
		CZ 9500565 A3	15-11-1995
		DE 69325658 D1	19-08-1999
		DE 69325658 T2	30-12-1999
		DK 658161 T3	29-11-1999
		EP 0658161 A1	21-06-1995
		EP 0960883 A1	01-12-1999
		ES 2133410 T3	16-09-1999
		FI 951004 A	03-03-1995
		FI 982413 A	06-11-1998
		WO 9405659 A1	17-03-1994
		GR 3030794 T3	30-11-1999
		HK 1012363 A1	05-05-2000
		HU 72639 A2	28-05-1996
		IL 106904 A	30-09-1997
		JP 11147885 A	02-06-1999
		JP 2828777 B2	25-11-1998
		JP 8501095 T	06-02-1996
		LU 90712 A9	12-03-2001
		MX 9305397 A1	31-01-1995
		NO 950852 A	03-03-1995
		NO 974646 A	03-03-1995
		NZ 255505 A	22-08-1997
		PL 307812 A1	26-06-1995
		RU 2128179 C1	27-03-1999
		SG 48302 A1	17-04-1998
		SI 9300452 A	30-06-1994
		SK 27795 A3	09-08-1995
		TW 385309 B	21-03-2000
		US 5741803 A	21-04-1998
		US 5910592 A	08-06-1999
		ZA 9306509 A	16-06-1994
WO 9727191 A	31-07-1997	AU 700976 B2	14-01-1999
		AU 2316497 A	20-08-1997
		CA 2248810 A1	31-07-1997
		CN 1196730 A	21-10-1998
		EP 0844997 A1	03-06-1998
		JP 2000511875 T	12-09-2000
EP 0306228 A	08-03-1989	WO 9727191 A1	31-07-1997
		AT 186724 T	15-12-1999
		AU 2173888 A	09-03-1989
		BR 1100841 A3	20-06-2000

INTERNATIONAL SEARCH REPORT

Information on patent family members

In International Application No

PCT/US 01/29896

Patent document cited in search report		Publication date	Patent family member(s)	Publication date		
EP 0306228	A		CA 1328452 A1	12-04-1994		
			CA 1339902 A1	09-06-1998		
			CZ 9103916 A3	17-03-1993		
			DE 3856378 D1	23-12-1999		
			DE 3856378 T2	11-05-2000		
			DK 490288 A	05-03-1989		
			DK 200001556 A	18-10-2000		
			EP 0306228 A1	08-03-1989		
			EP 0842925 A1	20-05-1998		
			ES 2137915 T3	01-01-2000		
			GR 3031873 T3	29-02-2000		
			HK 1011029 A1	03-11-2000		
			JP 10194970 A	28-07-1998		
			JP 10194971 A	28-07-1998		
			JP 1131169 A	24-05-1989		
			JP 2614497 B2	28-05-1997		
			JP 2817840 B2	30-10-1998		
			JP 9183771 A	15-07-1997		
			JP 2837139 B2	14-12-1998		
			JP 9183726 A	15-07-1997		
			JP 9183772 A	15-07-1997		
			KR 164207 B1	15-01-1999		
			KR 164275 B1	15-01-1999		
			KR 169463 B1	15-01-1999		
			LU 90711 A9	05-03-2001		
			NZ 226027 A	26-03-1992		
			PT 88410 A , B	31-07-1989		
			SG 59988 A1	22-02-1999		
			SK 391691 A3	11-12-2000		
			US 6288095 B1	11-09-2001		
			US 5646169 A	08-07-1997		
			US 5002953 A	26-03-1991		
			US 5521201 A	28-05-1996		
			US 5232925 A	03-08-1993		
			US 5194443 A	16-03-1993		
			US 5756525 A	26-05-1998		
			US 5260445 A	09-11-1993		
			ZA 8806536 A	26-07-1989		
		WO 9741120	A	06-11-1997	US 5801173 A	01-09-1998
					AU 2995497 A	19-11-1997
	CN 1221417 A			30-06-1999		
	EP 0923580 A1			23-06-1999		
	JP 2000514041 T			24-10-2000		
	WO 9741120 A1			06-11-1997		
	US 5919782 A			06-07-1999		